Remarks

Reconsideration and allowance are respectfully requested.

Claims 1-14 are pending in the application. Claims 6 and 12 have been objected to. Claims 1-14 have been rejected. Claim 6 has been cancelled.

Claims 6 and 12 have been objected to because the claims are identical. In response, Claim 6 has been cancelled. In view of the above, withdrawal of the objection of Claims 6 and 12 is respectfully requested.

Claims 1-14 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 9 of U.S. Patent No. 6,455,547.

In response before filing a terminal disclaimer, Applicants respectfully request that the Examiner confirm that Claims 1-14 are rejected as being unpatentable over only dependent Claim 9 of U.S. Patent No. 6,455,547.

Claims 1-14 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the translation of Kurasawa et al. (JP62277323 [JP'323]). In particular, the Examiner states:

> "Kurasawa teaches an ophthalmic solution comprising ketotifen fumarate, benzalkonium chloride, glycerol and water (See Abstract and Translation provided in the IDS). Kurasawa does not teach the exact concentrations recited in the instant application.
>
> While the reference does not teach the complete concentration range, differences in concentration will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 105 USPQ 233, 235 (CCPA 1955).
>
> At the time the invention was made, it would have been obvious to a person of ordinary skill in the art to prepare an ophthalmic solution comprising ketotifen fumarate, benzalkonium chloride, glycerol and water.
>
> One of ordinary skill in the art would have been motivated to do this to prepare an eye solution that is similar in composition to a tear to rewet the eyes of the host/patient. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made."

Applicants respectfully traverse and submit that JP '323 does not make obvious Claims 1-14 for the reasons stated below.

The arguments proffered in the previous Response dated November 15, 2002 to address this §103 rejection are reiterated here.

In particular, with respect to JP '323, this reference at Page 3, Example 1, describes the use of ketotifen fumarate in combination with an isotonizing agent, benzalkonium chloride and water as an eye water formulation. JP '323, however, does not teach these components, particularly ketotifen fumarate, i.e., ketotifen hydrogen fumarate, at the concentrations defined in independent Claims 1 and 7 or claims dependent therefrom. Indeed, JP '323 describes only one concentration of ketotifen fumarate 0.1%, i.e., 1 g in 1000 mL (g) of water, which is significantly higher, i.e., approximately three times that recited in independent Claims 1 and 7. Accordingly, there is no teaching or specific suggestion in JP '323 of the concentration of ketotifen hydrogen fumarate set forth in independent Claims 1 and 7 or that such a concentration would be efficacious in treating allergic conjunctivitis.

Other art of record (cited in PTO Form 1449) pertaining to ketotifen formulations and their use in treating allergic conjunctivitis is also devoid of any disclosure regarding use of the ketotifen hydrogen fumarate concentration recited in independent Claims 1 and 7.

For example, Kawasaki et al., *Iyakuhin Kenkyu*, Vol. 19, No. 5, pp. 821-826 (1988) and Kawasaki et al., *Iyakuhin Kenkyu*, Vol. 19, No. 5, pp. 827-838 (1988) (the Kawasaki et al. references), describe eye irritation studies on ketotifen fumarate-containing eye drops in rabbits.

The Kayasaki references disclose the concentration of the active agent not as the concentration of ketotifen fumarate, but rather as the concentration of ketotifen produced by making a particular solution of ketotifen fumarate. The molecular weight of ketotifen fumarate is 425.5. The molecular weight of ketotifen is 309.43. Thus, 1.38 times as much ketotifen fumarate will be necessary to yield a solution of a given concentration of ketotifen, e.g., a 0.345% solution of ketotifen fumarate will yield a 0.025% solution of ketotifen and a 0.069% solution of ketotifen fumarate will yield a solution that is 0.05% ketotifen. Similarly, to make a 0.8% solution of ketotifen, a 1.104% solution of ketotifen fumarate is necessary.

The Kayasaki references indicate that the eye drops used in the studies contain from 0.05-0.8% ketotifen fumarate as ketotifen (0.05% ketotifen equivalent to 0.069% ketotifen fumarate and 0.8% ketotifen equivalent to 1.104% ketotifen fumarate). There is no teaching or specific suggestion in either of the Kawasaki et al. references of utilizing a ketotifen fumarate solution containing a significantly lower concentration of ketotifen hydrogen fumarate, i.e., 0.0345%, as set forth in independent Claims 1 and 7.

Another example is Mikuni, *Rinshu Iyaku, J Clin Thera Med*, Vol. 4, No. 12, pp. 2371-2382 (1988) (Mikuni), which describes studies utilizing 0.05% ketotifen ophthalmic solution (equivalent to 0.069% ketotifen fumarate) to evaluate the efficacy and safety in treating patients with allergic conjunctivitis. In particular, the English translation of Mikuni on Page 8 indicates that there was improvement in ocular symptoms, such as itching utilizing 0.05% ketotifen. There is no teaching or specific suggestion in Mikuni to utilize a significantly lower concentration of ketotifen hydrogen fumarate, 0.0345% (equivalent to 0.025% ketotifen), as recited in independent Claims 1 and 7.

To summarize, JP '323, the Kawasaki et al. references and Mikuni are completely silent regarding the specific concentration, 0.0345%, of ketotifen hydrogen fumarate recited in independent Claims 1 and 7 for use in a composition to treat allergic conjunctivitis. Accordingly, the aforementioned references taken as a whole not only indicate that the state of the art does not teach or specifically suggest use of the claimed low concentration of ketotifen hydrogen fumarate but importantly, also show that only concentrations of 0.05% ketotifen (0.069% ketotifen fumarate) or higher were considered effective in treating allergic conjunctivitis.

Further support for the state of the art pertaining to ketotifen concentrations utilized in ophthalmic compositions to treat allergic conjunctivitis at the time of the priority date of the present application, January 15, 1998, has been previously presented by way of the attached Declaration of Andrea Fetz under 37 CFR 1.132, which was submitted in Case 4-31073A, Application Serial No. 09/619,349 ('349), filed July 19, 2000. In the declaration, Dr. Fetz states that prior to the priority date of the '349 application, July 23, 1999, ophthalmic solutions of 0.069% ketotifen fumarate yielding an effective 0.05% ketotifen concentration have been marketed in five other countries other than the U.S. Accordingly, the declaration makes clear that at the time of the priority date of the present application, the state of the art was such that administration of a ketotifen fumarate concentration of 0.069% was considered necessary to effectively treat allergic conjunctivitis.

To summarize, the state of the art as represented by objective evidence, i.e., JP '323, Kawasaki et al. references and Mikuni, together with the Fetz declaration, collectively show that one skilled in the art only considered utilizing ketotifen at concentrations of 0.05% or higher (0.069% ketotifen fumarate or higher) to effectively treat allergic conjunctivitis. Accordingly, one skilled in the art armed with knowledge of the art would not be motivated to utilize significantly lower concentrations of ketotifen fumarate ophthalmic solution, i.e., less than 0.069% ketotifen fumarate (0.05% ketotifen), to determine the optimal concentration of ketotifen fumarate necessary to effectively treat allergic conjunctivitis and arrive at the concentration of ketotifen hydrogen fumarate recited in independent Claims 1 and 7.

If the Examiner still maintains that a *prima facie* case of obviousness is established, then it is further submitted that a *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.

In this regard, Applicants respectfully direct the Examiner's attention to the Federal Court's instruction in *In re Gurley*, 31 USPQ2d 1131 (Fed. Cir. 1994), wherein the Court instructed that a prior art reference "teaches away" when one of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the prior art reference, or alternatively, would be led in a direction divergent from the path that was taken by the applicant.

In view of the above instruction, it can fairly be said that Fugita et al., Rinsho Iyaku, *J Clin Thera Med*, Vol. 5, No. 4, pp. 709-721 (1989) (Fugita et al., cited in PTO Form 1449) specifically teaches away from the concentration 0.0345% of ketotifen hydrogen fumarate recited in independent Claims 1 and 7.

Before discussing the specific studies described in Fugita et al., Applicants note that Fujita et al. disclose the concentration of the active agent not as the concentration of ketotifen fumarate, but rather as the concentration of ketotifen. As stated above, the molecular weight of ketotifen fumarate is 425.5. The molecular weight of ketoifen is 309.43. Thus, 1.38 times as much ketotifen fumarate will be necessary to yield a solution of a given concentration of ketotifen, e.g., a 0.025% ketotifen solution and 0.05% ketotifen solution as described in Fugita et al. are equivalent to a 0.0345% ketotifen fumarate solution and a 0.069% ketotifen fumarate solution, respectively.

Fugita et al. describe clinical studies which evaluated the efficacy and optimal concentration of ketotifen ophthalmic solution in treating allergic conjunctivitis. With respect to efficacy of ketotifen ophthalmic solutions in treating allergic conjunctivitis, Fujita et al. state on Page 1, fourth paragraph of the introduction, that previously "... excellent results were reported by multicenter cooperative research on 0.05% HC [ketotifen] ophthalmic solution in allergic conjunctivitis. On the other hand, the efficacy of HC ophthalmic solutions of concentrations lower than 0.05% has not been studied." Accordingly, in the studies presented by Fujita et al., the efficacy and safety of 0.05% and 0.025% HC ophthalmic solutions were compared.

The results of the Fugita et al. studies showed that a 0.05% ketotifen solution was significantly superior to a 0.025% ketotifen solution in terms of efficacy in treating allergic conjunctivitis. Specifically, the improvement rate of allergic conjunctivitis when using the 0.05% ketotifen solution was 85% whereas the improvement rate was only 23% when using the 0.025% ketotifen solution. Accordingly, one skilled in the art armed with the teaching of Fugita et al. would be led in a direction divergent from the path that was taken by the Applicants, that is, one skilled in the art would have chosen 0.05% ketotifen solution as the optimal

concentration instead of 0.025% ketotifen (equivalent to 0.0345% ketotifen fumarate- the concentration recited in the present claims).

In view of the findings of: 1) the absence of a specific suggestion in JP '323 or other art of record of the concentration of ketotifen hydrogen fumarate recited in the present claims; 2) the state of the art which collectively indicate that at the time the application was filed 0.05% or higher concentration of ketotifen (0.069% ketotifen fumarate) was considered necessary to effectively treat allergic conjunctivitis; and 3) the teaching away by Fugita et al. from the presently claimed concentration of ketotifen hydrogen fumarate, one skilled in the art would not have been motivated to carry out studies to optimize efficacy by utilizing ketotifen concentrations lower than 0.05% and thus arrive at the concentration recited in the present claims. Indeed, rather than motivating one skilled in the art to experiment with lower concentrations of ketotifen fumarate (0.069% or lower) to find the optimum concentration of ketotifen to treat allergic conjunctivitis, these findings would have had the general effect of deterring one skilled in the art from further experimentation. Accordingly, it is respectfully submitted that a *prima facie* case of obviousness has not been established.

It is further submitted that even if the Examiner has made a *prima facie* case of obviousness, evidence by way of the accompanying Declaration of Dr. Troy A. Reaves under 37 CFR 1.132 demonstrate the non-obviousness of the presently claimed invention, particularly the non-obviousness of utilizing the low concentration of ketotifen hydrogen fumarate recited in the present claims to treat allergic conjunctivitis.

As set forth in the declaration, Dr. Reaves supervised Phase II clinical studies which involved evaluating the efficacy, onset and duration of action of varying concentrations of ketotifen ophthalmic solution versus placebo utilizing the allergen challenge model, which is accepted by the USFDA as an appropriate surrogate to wild-type allergic conjunctivitis seen in humans. The following four concentrations of ketotifen ophthalmic solutions were utilized in the study: ketotifen 0.025% ophthalmic solution (equivalent to ketotifen fumarate 0.0345% weight/volume); ketotifen 0.05% ophthalmic solution (equivalent to ketotifen fumarate 0.069% weight/volume); ketotifen 0.1% ophthalmic solution (equivalent to ketotifen fumarate 0.138% weight/volume); and ketotifen 0.15% ophthalmic solution (equivalent to ketotifen fumarate 0.207% weight/volume). Using the allergen challenge model, subjects received one of the four concentrations of ketotifen solution at 15 minutes (Visit 3 - onset of action), 8 hours (Visit 4 - the first duration-of-action challenge) and 12 hours (Visit 5 - the second-duration-of-action challenge) prior to allergen challenge. Efficacy of treatment with the ketotifen solutions was measured by the relief of ocular itching in subjects at 3, 7, 10, 15 and 20 minutes after allergen challenge.

The results from these experiments (see Figures 1, 2, 3 and Table of Declaration) demonstrated that at Visits 3, 4 and 5 no apparent ordered-dose relationship was observed at any time point when determining the efficacy of the ketotifen solutions (0.025%, 0.05%, 0.1% and 0.15%) by the prevention of ocular itching induced in subjects by the allergen challenge model. Thus, the 0.025% ketotifen solution (equivalent to 0.0345% ketotifen fumarate, the concentration of ketotifen fumarate recited in the present claims) was found to be comparable in efficacy to the three other concentrations of ketotifen solution. The four concentrations of ketotifen solution were also found to have a comparable prolonged duration of action and prevented the development of the ocular itching response in eyes challenged with allergen over a 12-hour period. The findings of: 1) a lack of an ordered dose relationship among the four ketotifen concentrations indicating that 0.025% ketotifen solution was as efficacious as the other three ketotifen solutions; and 2) a prolonged duration of action observed for the 0.025% ketotifen solution that was comparable with the other three ketotifen solutions, were surprising and unexpected.

As noted in the Declaration, the surprising and unexpected nature of these findings is further supported by the Fugita et al. reference (see Exhibit C of the Declaration) which as discussed above demonstrated that the 0.025% ketotifen solution (equivalent to 0.0345% ketotifen fumarate) was significantly less efficacious when compared to the 0.05% ketotifen solution (equivalent to 0.069% ketotifen fumarate) in treating allergic conjunctivitis.

Accordingly, the evidence presented in the declaration demonstrate that it would have been non-obvious for one skilled in the art to utilize the concentration 0.0345% ketotifen hydrogen fumarate as recited in independent Claims 1 and 7.

In view of the above, withdrawal of the rejection of Claims 1-14 under 35 U.S.C. §103(a) is respectfully requested.

A good faith effort has been made to place the present application in condition for allowance.

If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned counsel at the number listed below.

Respectfully submitted,

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